HHS Public Access

Author manuscript

Pancreas. Author manuscript; available in PMC 2020 May 01.

Published in final edited form as:

Pancreas. 2019 ; 48(5): 594–597. doi:10.1097/MPA.0000000000001300.

Pathogenesis of Pancreatic Cancer-related Diabetes Mellitus: Quo Vadis?

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Introduction

In the Fall of 2018 the American Pancreas Association and the International Association of Pancreatology organized a special pre-meeting symposium on Pancreatitis and Pancreatic Cancer Associated Diabetes that included several outstanding State of the Art lectures. The basis of this invited review is the State of the Art lecture given by the author. It is focused on the pathogenesis of pancreatic cancer associated diabetes and where we may be headed given recent advances in our knowledge in this regard (*quo vadis*: Latin for “where are you marching”).

Background

Pancreatic ductal adenocarcinoma (PDAC) is a deadly, treatment-recalcitrant cancer with a propensity to metastasize, a dismal 5-year survival rate of ~9%, and a trajectory suggesting that it may become the second leading cause of cancer-related deaths in the United States in a few years.[1-2] In addition to a high frequency of major driver mutations, most notably mutated *KRAS*, deep whole genome sequencing and copy number variation studies revealed numerous low-frequency gene alterations, small regions of hypermutation termed kataegis, as well as deletions, rearrangements and amplifications of large DNA fragments, underscoring PDAC’s heterogeneous nature at the molecular level.[3-4] Nonetheless, at the molecular level, PDAC can be sub-classified into four subtypes that may have therapeutic relevance[4]. Crucially, at presentation, ~80% of patients with PDAC exhibit metastatic or locally invasive disease, precluding hope for a potential cure by resection.[5]

Because new-onset diabetes (NoD) at age 50 and above could be a harbinger of PDAC that precedes diagnosis by a few months to 3 years,[6] there is great deal of interest in assessing whether this population can be screened for NoD and whether these individuals could then be evaluated for early stage PDAC. Such an approach requires an understanding of type 2 diabetes (T2DM).

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The author declares no conflict of interest.

T2DM Statistics

According to the Centers for Disease Control, there were 30.3 million Americans with diabetes in 2015 and ~84 million Americans with pre-diabetes, defined as a fasting plasma glucose (FPG) of 100–125 mg/dl, or a 2 hour plasma glucose of 140–199 mg/dl, or a glycohemoblogin of 5.7 to 6.5%.[7] About 5% of individuals with pre-diabetes develop T2DM yearly. Amazingly, ~25% and ~88% of patients with diabetes and pre-diabetes, respectively, are not aware of their glycemic status.[7] There has also been a marked increase in obesity rates in the United States in recent decades, and obesity and T2DM often co-exist, yielding what has been called the “diabesity epidemic.”

Characteristics of T2DM

T2DM is characterized by four cardinal features. First, there is a state of insulin resistance that may be associated for many years with elevated circulating insulin levels reflecting compensatory mechanisms by the endocrine pancreas to combat hyperglycemia. Some patients may have inappropriately normal or slightly decreased insulin levels due beta cell exhaustion. Second, in all patients with established T2DM, the endocrine pancreas fails to produce sufficient quantities of insulin to overcome the resistance. Third, T2DM is associated with inappropriate and excessive hepatic glucose release, thereby exacerbating hyperglycemia and spurring the beta cell to produce and release more insulin. Fourth, the production of pro-inflammatory and diabetogenic adipokines by adipose tissues and resident macrophages enhances insulin resistance, further exacerbating demands on the beta cell. It has been estimated that each Kg of fat can harbor as many as 30 million macrophages,[8] underscoring the importance of weight control in the prevention and management of T2DM.

Mechanisms of Beta-Cell Failure in T2DM

Numerous pathways contribute to the beta cell failure in T2DM. Thus, prolonged increases in metabolic demands on the beta cells, along with chronic inflammation and endoplasmic reticulum stress[9-10] can all combine to interfere with beta cell function. The islets in T2DM develop peri-insular fibrosis that is infiltrated with activated macrophages,[11] leading to a pro-inflammatory milieu and propensity for vascular perturbations in the endocrine islets. Proper islet function requires certain islets to act as pacemakers that regulate rhythmic insulin secretion by adjoining islets.[12] Malfunction within this important islet hub regulatory axis can accelerate functional beta cell failure, which is further exacerbated by inefficient proinsulin processing. In addition there are genetic susceptibility factors that are multigenic and that include a propensity for fragile islets as has been known to exist in T1DM.[13]

Complex connections between Hyperglycemia, Diabetes, and PDAC

The pathophysiological connections between glycemic control and the risk for developing PDAC are complex. Longstanding T2DM is associated with ~2-fold increased risk for developing PDAC and there are likely additive deleterious effects with obesity.[14] In both conditions there is a systemic pro-inflammatory biology that may promote neoplastic transformation in the pancreas. In addition, T2DM and obesity are associated with chronic

hyperinsulinemia. There is also an islet-exocrine pancreas axis whereby some islets release insulin into a capillary bed that bathes adjoining acinar and ductal cells.[15] As a result of this intrapancreatic portal circulation certain regions of the exocrine pancreas are chronically exposed to super-physiological levels of insulin. Such high insulin levels within the pancreatic microenvironment are able to activate the insulin-like growth factor (IGF-1) receptor (IGF-1R) and may thus exert mitogenic effects in early pre-neoplastic lesions in the pancreas and promote their survival.

T1DM is also associated with hyperglycemia but with exceedingly low circulating insulin levels. Although T1DM does not appear to lead to an increased incidence of PDAC, this issue has not been completely resolved due to the smaller number of patients with T1DM by comparison with T2DM, and the reliance in some studies on age at diagnosis to define T1DM. Since T2DM may occur in the second and third decade of life, and in the past 20 years in and increasing number of teenagers, an age for diabetes onset that is less than 30 or 40 years as the cut-off is not an adequate sole criterion for concluding that an individual has T1DM. In an extensive meta-analysis of numerous studies only 11 patients with a definitive diagnosis of T1DM developed PDAC.[16] Moreover, a large cohort study of 29,187 individuals in Sweden in which the mean age at the time of first hospitalization for T1DM was 17.1 years used several criteria for designating patients as having T1DM and relied on the use of extensive medical records in the Swedish health care system.[17] This study did not find an increased incidence of PDAC in T1DM. These observations are consistent with the hypothesis that chronic endogenous hyperinsulinemia contributes to the increased incidence of PDAC in patients with long-standing T2DM and that T1DM is not associated with an increased PDAC incidence.

Most commonly, in patients with PDAC loss of glycemic control is caused by the presence of the cancer. Importantly, new-onset diabetes (NoD) at age 50 or older may develop a few weeks or months and even 2–3 years prior to the clinical diagnosis of PDAC, and may thus be a tell-tale sign of the underlying malignancy.[6,18-19] Overall, ~1% of individuals with NoD in this age group will be diagnosed with PDAC. However, this frequency warrants confirmation given the high number of individuals with T2DM and pre-diabetes in the United States. Accordingly, a large scale longitudinal study was initiated through the NIH-funded multi center Consortium for the Study of Chronic Pancreatitis, Diabetes and Pancreatic Cancer.[20] Only PDAC is associated with NoD, and nearly 50% of patients with PDAC may have a FBG that is greater than 125 mg/dl,[21] underscoring the importance of this paraneoplastic manifestation of PDAC, the urgent need to understand the underlying mechanisms, and the imperative to use this knowledge to devise strategies that will allow for early stage diagnosis.

Pathogenesis of PDAC-Associated NoD

New-onset diabetes caused by PDAC is associated with pro-inflammatory alterations, insulin resistance, and perturbations in beta cell functions that lead to loss of glucose homeostasis. Adipocytes and resident macrophages release many deleterious pro-inflammatory factors and the increased lipolysis could enhance hepatic production of acetyl co-A that causes hepatic insulin resistance and excessive glucose release by the liver.[22] The tumor may also

produce factors that enhance resistance to insulin action in muscle and adipose tissues, given that resection of small tumors while sparing the pancreas tail which is rich in islets may eliminate the diabetes by improving insulin sensitivity.[23]

Islet blood flow dysfunction, microthrombosis, and peri-vascular fibrosis may be seen in PDAC, and likely combine to suppress the ability of the beta cell to exhibit normal insulin secretory dynamics in NoD. Islet blood flow is “leaky” due physiological fenestrations, but this may be enhanced by the above perturbations thereby worsening intra-pancreatic insulin stasis. These very high insulin levels excessively activate both the insulin receptor and the IGF-1 receptor, leading to enhanced survival of pre-malignant cells, greater cancer cell proliferation, and apoptosis resistance.

NoD May Accelerate PDAC Progression

It is now recognized that once PDAC is diagnosed clinically it tends to exhibit accelerated progression.[24] Patients with NoD may exhibit a deterioration in their ability to normalize glucose levels with medication, perhaps because their cancer is now in an accelerated growth phase. More rapid tumor growth could be secondary to an enhanced pro-inflammatory state systemically, increased acetyl co-A levels that may promote mitogenesis and autophagy, high lipocalin-2 levels in the tumor that contribute to a pro-inflammatory tumor microenvironment (TME), and overexpression of galectin 3 that can lead to enhanced Kras activation.[22, 25-27] Moreover, islets produce insulin and pancreatic cancer cells and associated stroma produce IGF1, and both factors stimulate mitogenic signaling in pancreatic cancer cells.

Clinical and Mechanistic Points

Clinically, NoD may present with rising blood glucose levels in spite of weight loss, a combination that is not often seen in T2DM. There may also be a sudden deterioration in glycemic control in misdiagnosed patients that were thought to have T2DM but had NoD. PDAC is also associated with release of abnormal exosomes that may carry factors such as adrenomedullin that causes beta cell dysfunction[28] and activation of mitogen activated protein kinase (MAPK) and p38-MAPK in adipocytes, leading to enhanced lipolysis in adipocytes[29]. Pancreatic cancer cell derived exosomes also induce insulin resistance in skeletal muscle, as can be extrapolated from the observation that such exosomes inhibit insulin-PI3K-Akt signaling in C2C12 myotubes and thereby interfere with GLUT4 uptake.[30] However, NoD often precedes clinical evidence for cachexia, suggesting that cachexia is not the etiology for NoD. Crucially, tumor resection restores insulin sensitivity, raising the possibility that PDAC exosomes may contribute to insulin resistance, beta cell failure, and lipolysis, thereby explaining the high incidence of NoD in PDAC. NoD can thus be viewed, in part, as a PDAC-associated exosomopathy.[31]

Given the above issues, the potential roles of the TME, immune system, cancer-associated adipocytes, the microbiome and PDAC-associated exosomes need to be further explored. Moreover, technological improvements suggest that analysis of the cargo in liquid biopsy

derived exosomes could be used to establish diagnostic signatures and DNA mutation status, generate prognostic and recurrence signatures, and provide therapeutic guidance.

Beneficial Consequences of Early Diagnosis

The benefits of early diagnosis remain to be proven. In theory, however, diagnosing PDAC when it is stage IA or pre-stage 1A (microscopic disease) could dramatically increase cure rates and long-term survival. Moreover, specific biomarker signatures could be useful for monitoring disease recurrence, which will further prolong survival. Some circulating biomarkers may also allow for patient stratification into more effective targeted therapies. Previously proposed screening strategies for NOD could thus lead to a markedly improved prognosis to patients with PDAC.[32]

Practical Considerations

Unfortunately, neither the medical community nor the susceptible patient populations are generally aware of NoD. An analysis of health care utilization prior to PDAC diagnosis revealed that 42% of ~1000 patients had few physician encounters during the 36 months prior to PDAC diagnosis and these occurred during the 6 months prior to diagnosis, whereas other groups had early or early and persistent interactions with health care providers.[33] Therefore, it is important to educate the public and health care providers such as internists, family doctors, endocrinologists, gastroenterologists, physician assistants, nurses, and other health care professionals about NoD.

Conclusion

Pancreatic ductal adenocarcinoma is not a rare cancer. According to the American Cancer Society, the lifetime risk for getting pancreatic cancer in the United States is one in 63 men and one in 64 women. Due to its treatment-recalcitrant behavior, PDAC is currently the third leading cause of cancer death in the United States. Fortunately, the entire world-wide scientific community has taken advantage of novel technologies, team science that has included international collaborations, and increased funding by the NIH as well as several critically important foundations. Marching toward a better understanding of NOD, risk factors, diagnostic and prevention strategies, population susceptibilities, and combinatorial therapeutic modalities should soon be translated into dramatically improved survival statistics.

Acknowledgments

Supported, in part, by National Cancer Institute Grant CA-075059.

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